

General

Guideline Title

The role of postoperative radiation therapy for endometrial cancer: an ASTRO evidence-based guideline.

Bibliographic Source(s)

Klopp A, Smith BD, Alektiar K, Cabrera A, Damato AL, Erickson B, Fleming G, Gaffney D, Greven K, Lu K, Miller D, Moore D, Petereit D, Scheffer T, Small W Jr, Yashar C, Viswanathan AN. The role of postoperative radiation therapy for endometrial cancer: an ASTRO evidence-based guideline. *Pract Radiat Oncol*. 2014;(Suppl):1-22. [47 references]

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

The American College of Physicians (ACP) process for assigning strength of Recommendation (Strong, Weak) and grading of quality of evidence (High, Moderate, and Low-Quality) is defined at the end of the "Major Recommendations" field.

Key Question (KQ) 1 Guideline Statement: Which Patients with Endometrioid Endometrial Cancer Require No Additional Therapy After Hysterectomy?

Following total abdominal hysterectomy (TAH) with or without node dissection, no radiation therapy is a reasonable option for patients with: (1) no residual disease in the hysterectomy specimen despite positive biopsy (grade: strong recommendation, low-quality evidence) or (2) grade 1 or 2 cancers with either no invasion or <50% myometrial invasion, especially when no other high-risk features are present (grade: strong recommendation, high-quality evidence). Patients with the following pathologic features may be reasonably treated with or without vaginal brachytherapy: (1) grade 3 cancers without myometrial invasion (grade: strong recommendation, low-quality evidence) or (2) grade 1 or 2 cancers with <50% myometrial invasion and higher-risk features, such as age >60 and/or lymphovascular space invasion (LVSI) (grade: strong recommendation, moderate-quality evidence). See Table 1 in the original guideline document for consensus/percent agreement.

KQ2 Guideline Statement: Which Patients with Endometrioid Endometrial Cancer Should Receive Vaginal Cuff Radiation?

Vaginal cuff brachytherapy is as effective as pelvic radiation therapy at preventing vaginal recurrence for patients with: (1) grade 1 or 2 cancers with ≥50% myometrial invasion or (2) grade 3 tumors with <50% myometrial invasion (grade: strong recommendation, moderate-quality evidence). Vaginal cuff brachytherapy is preferred to pelvic radiation in patients with these risk factors, particularly in those patients who have had comprehensive nodal assessment (grade: strong recommendation, low-quality evidence). See Table 1 in the original guideline document for consensus/percent agreement.

KQ3 Guideline Statement (A): Which Women with Early-Stage Endometrial Cancer Should Receive Postoperative External Beam Radiation?

Pelvic radiation is an effective means of decreasing pelvic recurrence for early-stage patients but has not been proven to improve overall survival. Patients with grade 3 cancer with $\geq 50\%$ myometrial invasion or cervical stromal invasion may benefit from pelvic radiation to reduce the risk of pelvic recurrence (grade: strong recommendation, high-quality evidence). Patients with grade 1 or 2 tumors with $\geq 50\%$ myometrial invasion may also benefit from pelvic radiation to reduce pelvic recurrence rates if other risk factors are present, such as age >60 years and/or LVSI (grade: strong recommendation, high-quality evidence).

KQ3 Guideline Statement (B): Which Women with Stage III-IVA Endometrial Cancer Should Receive Postoperative External Beam Radiation? The Use of Pelvic Radiation Has Been Shown to Improve Survival in Some Settings.

The best available evidence at this time suggests that a reasonable option for adjuvant treatment of patients with positive nodes or involved uterine serosa, ovaries/fallopian tubes, vagina, bladder, or rectum includes external beam radiation therapy as well as adjuvant chemotherapy (grade: strong recommendation, moderate-quality evidence). Chemotherapy (grade: weak recommendation, moderate-quality evidence) or radiation therapy alone (grade: weak recommendation, low-quality evidence) may be considered for some patients based on pathologic risk factors for pelvic recurrence. See Table 1 in the original guideline document for consensus/percent agreement.

KQ4 Guideline Statement: When Should Brachytherapy Be Used in Addition to External Beam Radiation?

Prospective data is lacking to validate the use of vaginal brachytherapy after pelvic radiation and retrospective studies show little conclusive evidence of a benefit, albeit with small patient numbers. Use of vaginal brachytherapy in patients also undergoing pelvic external beam radiation may not generally be warranted, unless risk factors for vaginal recurrence are present (grade: weak recommendation, low-quality evidence). See Table 1 in the original guideline document for consensus/percent agreement.

KQ5 Guideline Statement: How Should Radiation Therapy and Chemotherapy be Integrated in the Management of Endometrial Cancer?

The best available evidence suggests that concurrent chemoradiation followed by adjuvant chemotherapy is indicated for patients with positive nodes or involved uterine serosa, ovaries/fallopian tubes, vagina, bladder, or rectum (grade: strong recommendation, moderate quality evidence). Alternative sequencing strategies with external beam radiation and chemotherapy are also acceptable (grade: weak recommendation, low-quality evidence). Chemotherapy (moderate-quality evidence) or radiation therapy alone (low-quality evidence) may be considered for some patients based on pathologic risk factors for pelvic recurrence. See Table 1 in the original guideline document for consensus/percent agreement.

Definitions:

ACP Process for Grading of Quality of Evidence

High-Quality Evidence

Evidence is considered high quality when it is obtained from 1 or more well-designed and well-executed randomized, controlled trials (RCTs) that yield consistent and directly applicable results. This also means that further research is very unlikely to change confidence in the estimate of effect.

Moderate-Quality Evidence

Evidence is considered moderate quality when it is obtained from RCTs with important limitations—for example, biased assessment of the treatment effect, large loss to follow-up, lack of blinding, or unexplained heterogeneity (even if it is generated from rigorous RCTs). It also includes indirect evidence originating from similar (but not identical) populations of interest and RCTs with a very small number of participants or observed events. In addition, evidence from well-designed controlled trials without randomization, well-designed cohort or case-control analytic studies, and multiple time series with or without intervention are in this category. Moderate-quality evidence also means that further research will probably have an important effect on confidence in the estimate of effect and may change the estimate.

Low-Quality Evidence

Evidence obtained from observational studies would typically be rated as low quality because of the risk for bias. Low-quality evidence means that further research is very likely to have an important effect on our confidence in the estimate of effect and will probably change the estimate. However, the quality of the evidence from observational studies may be rated as moderate or even high, depending on circumstances under which evidence is obtained. Factors that may contribute to upgrading the quality of evidence include a large magnitude of the observed effect, a dose-response association, or the presence of an observed effect when all plausible confounders would decrease the observed effect.

ACP Process for Assigning Strength of Recommendation

Strong Recommendation

Evidence suggests that the benefit of the intervention outweighs the risk, and the panel has reached uniform consensus.

Weak Recommendation

Evidence suggests that the benefit of the intervention equals the risk, or vice versa, and the panel has reached uniform or nonuniform consensus.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Endometrial cancer

Guideline Category

Evaluation

Treatment

Clinical Specialty

Obstetrics and Gynecology

Oncology

Radiation Oncology

Intended Users

Physicians

Guideline Objective(s)

To provide evidence-based guidelines for adjuvant radiation in the treatment of endometrial cancer

Target Population

Women of all races, aged 18 years or older, with stage I-IV endometrial cancer of any histologic grade

Interventions and Practices Considered

1. No radiation therapy
2. Vaginal cuff brachytherapy
3. Pelvic radiation (postoperative external beam radiation)
4. Combination vaginal brachytherapy and pelvic radiation
5. Chemotherapy alone

6. Radiation therapy and chemotherapy integration
 - Concurrent chemoradiation followed by adjuvant chemotherapy
 - Alternative sequencing strategies with external beam radiation and chemotherapy

Major Outcomes Considered

- Survival rates
- Local and distant recurrence rates
- Toxicity
- Overall assessment of quality of life

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

An analytic framework, based on the identified population, interventions, comparators, and outcomes (PICO) was used to refine the search. The population was defined as women of all races, aged 18 years or older, with stage I-IV endometrial cancer of any histologic grade. A search was conducted for studies that included patients treated with no adjuvant therapy, or pelvic and/or vaginal brachytherapy with or without systemic chemotherapy. To assess the interventions employed by the studies, a literature search based on the following outcomes was conducted: survival rates, local and distant recurrence rates, toxicity, and overall assessment of quality of life. Exclusion criteria included trials of preoperative radiation therapy (RT), patients with distant metastasis, and patients with unresected gross residual disease after hysterectomy. Literature searches were performed on electronic databases that included "English only" literature from 1980 to 2011: MEDLINE PubMed, EMBASE, and the Specialized Register of the Cochrane Gynaecological Cancer Review Group (CGCRG). Additionally, reference lists of previous systematic reviews and other relevant papers were searched. Randomized clinical trials, nonrandomized clinical trials, observational studies, abstracts, and conference proceedings were searched as well. The initial search yielded 1077 abstracts. Articles were reviewed for inclusion by American Society for Radiation Oncology (ASTRO) staff and co-chairs of the guideline. Next, 148 articles were excluded due to small sample size, distant metastatic disease, medically inoperable patients, management of recurrences, and not being clinically relevant to the key questions. A second assessment resulted in the exclusion of 599 articles due to duplicate studies, sarcoma, studies involving less than 10 patients and studies not being clinically relevant to the key clinical questions.

Number of Source Documents

A total of 330 articles were fully abstracted to provide supporting evidence for the clinical guideline recommendations.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

American College of Physicians (ACP) Process for Grading of Quality of Evidence

High-Quality Evidence

Evidence is considered high quality when it is obtained from 1 or more well-designed and well-executed randomized, controlled trials (RCTs) that yield consistent and directly applicable results. This also means that further research is very unlikely to change confidence in the estimate of effect.

Moderate-Quality Evidence

Evidence is considered moderate quality when it is obtained from RCTs with important limitations—for example, biased assessment of the treatment effect, large loss to follow-up, lack of blinding, or unexplained heterogeneity (even if it is generated from rigorous RCTs). It also includes indirect evidence originating from similar (but not identical) populations of interest and RCTs with a very small number of participants or observed events. In addition, evidence from well-designed controlled trials without randomization, well-designed cohort or case-control analytic studies, and multiple time series with or without intervention are in this category. Moderate-quality evidence also means that further research will probably have an important effect on confidence in the estimate of effect and may change the estimate.

Low-Quality Evidence

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Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review

Description of the Methods Used to Analyze the Evidence

The body of evidence was categorized by the American College of Physicians (ACP) Strength of Evidence Rating. The ACP's ratings consist of high quality, moderate-quality, low quality, or insufficient evidence to determine net benefits or risks (see the "Rating Scheme for the Strength of the Evidence" field).

Methods Used to Formulate the Recommendations

Expert Consensus (Delphi)

Description of Methods Used to Formulate the Recommendations

The Guidelines Subcommittee of the Clinical Affairs and Quality Council, in accordance with established American Society for Radiation Oncology (ASTRO) policy, recruited a guideline panel of recognized experts in endometrial cancer including radiation oncologists (including one resident member), gynecologic oncologists, and radiation physicists in academic settings and private practice. The panel provided guidance on the use of radiation therapy for patients with endometrial cancer. In February 2011, the ASTRO Board of Directors approved the *Postoperative Radiation Therapy for Endometrial Cancer Guideline* proposal and panel membership. Next, the panel participated in a series of communications by electronic mail and conference telephone calls to draft the guideline. Members of the panel were divided into subgroups, according to their areas of expertise, to address the key questions (KQs). All members of the panel evaluated the responses to the questions assigned to the subgroups, according to their areas of expertise, to address the KQs. All members of the panel evaluated the responses to the questions assigned to the subgroups.

When available, high-quality evidence formed the basis of the recommendation statements in accordance with the Institute of Medicine (IOM) standards. Guideline statements were developed and included evidence ratings. The level of consensus on the guideline recommendation statements among the panelists was evaluated through a modified Delphi approach. The survey including guideline recommendation statements was sent by the American Society for Radiation Oncology (ASTRO) staff to the panel members. Panelists rated the agreement with each

recommendation pertaining to the key clinical questions on a 5-point Likert scale, ranging from strongly disagree to strongly agree, as depicted in Table 1 in the original guideline document (higher score corresponds with stronger agreement); a prespecified threshold of $\geq 75\%$ of raters was determined to indicate when consensus was achieved.

Rating Scheme for the Strength of the Recommendations

American College of Physicians (ACP) Process for Assigning Strength of Recommendation

Strong Recommendation

Evidence suggests that the benefit of the intervention outweighs the risk, and the panel has reached uniform consensus.

Weak Recommendation

Evidence suggests that the benefit of the intervention equals the risk, or vice versa, and the panel has reached uniform or nonuniform consensus.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The initial draft of the manuscript was reviewed by 3 expert reviewers and American Society for Radiation Oncology (ASTRO) legal counsel. A revised draft was placed on the ASTRO website in May 2013 for a 6-week public comment period. Following integration of feedback, the document was submitted for approval to the ASTRO Board of Directors in September 2013.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of postoperative radiation therapy in the treatment of endometrial cancer

Potential Harms

- Vaginal brachytherapy doesn't address the paravaginal tissues and draining lymphatics. The side effects of vaginal cuff irradiation are generally limited to vaginal complications and mild urinary side effects. Nine percent of patients in a randomized trial receiving brachytherapy developed grade 1 and 2 vaginal toxicity as compared to 1.5% of patients in the observation arm. Grade 1 and 2 urinary side effects were slightly more common after vaginal irradiation (2.8% vs 0.6%, respectively, $P = .063$) but brachytherapy did not impact the rates of

gastrointestinal (GI) toxicity. Brachytherapy dose has been shown to impact vaginal toxicity.

- Grade 2 or higher diarrhea affects 50% to 80% of patients receiving pelvic radiation during and in the immediate posttreatment period.
- Some studies have reported higher rates of toxicity among patients receiving both brachytherapy and external beam. The addition of brachytherapy to pelvic radiation also increased the risk of second primary cancers in a Surveillance, Epidemiology, and End Results (SEER) study.

Qualifying Statements

Qualifying Statements

This document was prepared by the Endometrial Guideline Panel. The American Society for Radiation Oncology (ASTRO) guidelines present scientific, health, and safety information and may to some extent reflect scientific or medical opinion. They are made available to ASTRO members and to the public for educational and informational purposes only. Any commercial use of any content in this guideline without the prior written consent of ASTRO is strictly prohibited. Adherence to this guideline will not ensure successful treatment in every situation. Furthermore, this guideline should not be deemed inclusive of all proper methods of care or exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding the propriety of any specific therapy must be made by the physician and the patient in light of all circumstances presented by the individual patient. ASTRO assumes no liability for the information, conclusions, and findings contained in its guidelines. In addition, this guideline cannot be assumed to apply to the use of these interventions performed in the context of clinical trials, given that clinical studies are designed to evaluate or validate innovative approaches in a disease for which improved staging and treatment are needed or are being explored. This guideline was prepared on the basis of information available at the time the panel was conducting its research and discussions on this topic. There may be new developments that are not reflected in this guideline, and that may, over time, be a basis for ASTRO to consider revisiting and updating the guideline.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2014

Guideline Developer(s)

American Society for Radiation Oncology - Professional Association

Source(s) of Funding

American Society of Radiation Oncology

Guideline Committee

Endometrial Guideline Panel

Composition of Group That Authored the Guideline

Panel Members: Ann Klopp, MD, PhD, Department of Radiation Oncology, University of Texas MD Anderson Cancer Center, Houston, Texas; Benjamin D. Smith, MD, Department of Radiation Oncology, University of Texas MD Anderson Cancer Center, Houston, Texas; Kaled Alektiar, MD, Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, New York; Alvin Cabrera, MD, Department of Radiation Oncology, Duke University Medical Center, Durham, North Carolina; Antonio L. Damato, PhD, Department of Radiation Oncology, Dana-Farber Cancer Institute and Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; Beth Erickson, MD, Department of Radiation Oncology, Medical College of Wisconsin, Milwaukee, Wisconsin; Gini Fleming, MD, Department of Medicine, University of Chicago, Chicago, Illinois; David Gaffney, MD, PhD, Department of Radiation Oncology, University of Utah, Salt Lake City, Utah; Kathryn Greven, MD, Department of Radiation Oncology, Wake Forest University, Winston-Salem, North Carolina; Karen Lu, MD, Department of Gynecologic Oncology, University of Texas MD Anderson Cancer Center, Houston, Texas; David Miller, MD, Department of Obstetrics and Gynecology, University of Texas Southwestern Medical Center, Dallas, Texas; David Moore, MD, Franciscan Alliance, Mishawaka, Indiana; Daniel Petereit, MD, Regional Cancer Care Institute, Rapid City, South Dakota; Tracey Scheffer, MD, Department of Radiation Oncology, University of Colorado–Denver, Aurora, Colorado; William Small Jr., MD, Department of Radiation Oncology, Stritch School of Medicine, Loyola University, Chicago, Illinois; Catheryn Yashar, MD, Department of Radiation Oncology, University of California–San Diego, San Diego, California; Akila N. Viswanathan, MD, MPH (*Corresponding Author*), Department of Radiation Oncology, Dana-Farber Cancer Institute and Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

Financial Disclosures/Conflicts of Interest

Before initiation of this guideline, all members of the guideline panel were required to complete disclosure statements. These statements are maintained at the American Society for Radiation Oncology (ASTRO) headquarters in Fairfax, VA and pertinent disclosures are published with the report. The ASTRO Conflict of Interest Disclosure Statement seeks to provide a broad disclosure of outside interests. Where a potential conflict is detected, remedial measures to address any potential conflict are taken and will be noted in the disclosure statement. Ann Klopp, MD, PhD, has research funding from the Ovarian Cancer Research Foundation and the MD Anderson Cancer Center Endometrial and Ovarian Spore. Benjamin Smith, MD, has received research grants from Conquer Cancer Foundation and Cancer Prevention and Research Institute of Texas. He also serves as a consultant for Conquer Cancer Foundation. Akila Viswanathan, MD, is principal investigator for NIH R21 167800. Catheryn Yashar, MD, serves as a consultant to and owns stock in Cianna Medical. The guideline panel chairs, as well as the chair of the guideline subcommittee, reviewed these disclosures and determined that they do not present a conflict with respect to these panel members' work on this guideline.

Guideline Endorser(s)

Society of Gynecologic Oncology - Disease Specific Society

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the [American Society for Radiation Oncology \(ASTRO\) Web site](#) .

Availability of Companion Documents

The following is available:

- Klopp A, Smith BD, Alektiar K, Cabrera A, Damato AL, Erickson B, Fleming G, Gaffney D, Greven K, Lu K, Miller D, Moore D, Petereit D, Scheffer T, Small W Jr, Yashar C, Viswanathan AN. The role of postoperative radiation therapy for endometrial cancer: executive summary of an American Society for Radiation Oncology evidence-based guideline. Pract Radiat Oncol. 2014 May-Jun;4(3):137-44. Electronic copies: Available from the [American Society for Radiation Oncology \(ASTRO\) Web site](#)

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Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on July 2, 2014. The information was verified by the guideline developer on July 31, 2014.

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